Original Article

Gastric Cancer Mortality in a High Incidence Area: Long-term follow-up of Helicobacter pylori-related Precancerous Lesions in the General Population

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Abstract

Background: Due to a lack of clear criteria for recognizing subjects at risk of progression to gastric cancer (GC), this cohort study seeks to identify predictors of GC death in a high-risk population.

Methods: During 2000–2001, 1011 randomly selected residents of Ardabil, Iran without a history of gastrointestinal diseases, underwent upper endoscopy with targeted biopsy sampling. Until 2013, cancer mortality data were obtained using cancer and death registry data and verbal autopsy reports. Cox regression was used to estimate hazard ratios (HR).

Results: A total of 3.95% of the participants [mean age: 53.1 ± 9.9 years, 49.8% males, and 88.2% *Helicobacter pylori (H. pylori)*-positive] died of GC. In the multivariate model, precancerous lesions at the beginning of follow-up were associated with increased GC mortality. The HR [95% confidence interval (CI)] was 7.4 (1.6–33.8) for atrophic gastritis (AG) and 23.6 (5.5–102.3) for intestinal metaplasia (IM). Age over 50 (HR = 4.4; 1.3–14.2), family history of GC (HR = 6.8; 3.3–13.8), smoking (HR = 7.4; 3.2–17.3), and endoscopically confirmed gastric ulcer (GU, HR = 6.5; 2.5–16.4) were independently associated with GC mortality. The concomitant presence of a precancerous lesion increased the HR to 46.5 (10.8–198.6) for a family history of GC, 27.6 (6.5–116.4) for smoking, and 25.1 (6.3–105.3) for age >50 years.

Conclusion: In this population with a high rate of *H. pylori* infection, age over 50 years, smoking, family history of GC, IM, AG, and in particular, an undiagnosed GU were significant independent risk factors for mortality due to GC. The assessment of a combination of these risk factors might identify individuals at risk of GC who could possibly benefit from regular surveillance.

Keywords: Cohort study, gastric cancer, *Helicobacter pylori*, precancerous lesions, risk factors

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Introduction

A dramatic decline in the incidence and mortality of gastric cancer (GC) has been observed in recent decades; however, this ominous disease still prevails as the fourth most frequently occurring malignancy as well as the second cause of cancer-related death worldwide.[1] The problem is most conspicuous in developing countries, particularly in Asian countries, where 75% of all GC occur.[1–3] In Iran, GC is an important healthcare challenge with 10000 incident cases and 8000 deaths per year.[4] Ardabil Province in Northwest Iran has the highest incidence of GC in Iran and one of the highest rates of this cancer in the world, with age-standardized incidence rates (ASR) of 51.8 in men and 24.9 in women. Recent reports suggest that despite the mentioned worldwide trend, the rate of GC is still increasing in Ardabil.[5–9]

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While *Helicobacter pylori (H. pylori)* has been accepted as a definitive carcinogen,[10] an inconsistency between its prevalence and cancer occurrence called "The African Enigma" has been observed. This phenomenon refers to the lower risk of GC among some Asian and African populations, despite substantially high rates of *H. pylori* infection.[10–14] These observations indicate that although *H. pylori* is necessary for the development of GC, it is not sufficient for it. This suggests a prominent role for other GC risk factors and undermines the reliability of *H. pylori* preventive and eradication strategies in adult subjects.

GC is an insidious disease, often manifesting its symptoms at an advanced stage when few therapeutic options are available with even less efficiency. The sluggish process, known as Correa's cascade[15] passes through a series of intermediate stages (precancerous lesions) before reaching full-blown malignancy. These precancerous lesions occur in the following order: gastritis, atrophy, intestinal metaplasia (IM), and eventually dysplasia. Establishing a screening program has always been of interest in the case of GC and these precancerous lesions may prove outstanding candidates for this purpose. Therefore, we have conducted a current population-based, follow-up survey to investigate the role of precancerous lesions in GC mortality as well as identifying individuals at high risk of GC in an unselected general population living in an area with a high prevalence of *H. pylori* infection west of Asia.

Materials and Methods

Study environment

Participants were selected from two major regions of Ardabil Province, namely the townships of Ardabil and Meshkinshahr. We used a simple random household selection in urban and rural areas. Subsequently, we selected a participant aged 40 years or more who met the inclusion criteria from each family. If the criteria for selected participants were not met, the adjacent neighbor to the right was considered as a choice for study participation. Exclusion criteria were participant refusal for any reason, previous history of clinical workup for gastrointestinal (GI) disorders (except for mild symptoms of dyspepsia which entailed no definite diagnosis and required no medical therapy), pregnancy, and/or cardiopulmonary diseases. We provided thorough and clear information to all participants regarding the potential benefits and risks of the study, and all participants expressed their voluntary, informed consent in written. A total of 1011 individuals accepted the conditions of the study and each consented to an endoscopy procedure. The clinic is the major provider for GI diagnostic and therapeutic services in Ardabil Province. All subjects were free to refer to Aras Clinic or any other physician or clinic for gastrointestinal workups, if necessary.

Baseline assessment

The participants were interviewed by trained physicians about their demographics, lifestyle habits, tobacco, alcohol or drug use, history of upper GI cancer in first-degree relatives, and history of GI symptoms.

Subsequently, each participant underwent an upper GI endoscopy following a standardized protocol. Biopsy specimens were obtained from the incisura angularis, the lesser and greater curvatures of the antrum, the lesser and greater curvatures of the corpus, and the cardia. In addition, biopsy was taken from any visible lesions noted during endoscopy. Specimens from the incisura angularis were used for rapid urease test to detect *H. pylori* infection. All biopsies were oriented over small pieces of filter paper and immediately submerged in neutral buffered formalin in appropriately labeled containers. The process of tissue orientation, fixation, labeling, and recording was supervised by the pathologists in charge. Histological diagnoses were made using 3 μm thick sections stained by the hematoxylin and eosin method, and read by three pathologists experienced in gastrointestinal pathology. The pathologists were blinded to the endoscopic and clinical findings. The histological results were categorized based on The Updated Sydney Classification of Gastritis.[16]

Ascertainment of death due to gastric cancer (GC) during follow-up

At the start of the cohort study, we established a population-based cancer and death registry in Ardabil Province in collaboration with the International Agency for Research on Cancer (IARC) and the Ardabil University of Medical Sciences.[4,17] From the year 2000 onwards, data from these registries has been searched regularly to provide the time and cause of death of the participants, including cancer-related events. As for participants not registered in these systems, trained physicians contacted participants or their next of kin for health information. If the cause of death was uncertain, further assessments were undertaken with use of a modified version of the WHO adult verbal autopsy.[18] Trained staff collected the available medical documents of the participants, and the final cause of death was determined by two physicians who independently reviewed the collected medical records and verbal autopsy forms. The results were confirmed by two additional internists.

The Medical Ethics Committee of the Digestive Disease Research Centre of the Tehran University of Medical Sciences approved the protocol of this study.

Data analysis

The descriptive data are presented as frequencies and means ± standard deviations (SD). The differences between groups were analyzed with a *t*-test for continuous variables and with a Chi-square test for categorical variables. Entry time was defined as the enrollment date. End of follow-up was defined as the date of GC-related death, censoring, or the end of the follow-up (January 1, 2013), whichever came first. Univariate and multivariate Cox proportional hazard regression analyses were performed to assess the association between GC mortality and baseline precancerous lesions and risk factors. The magnitudes of associations are presented as hazard ratios (HR) and the corresponding 95% confidence intervals (95% CI). Age was classified into three categories (40–50, 51–60, and 61 or above), whereas the first category was the reference group. Histological changes in each individual were determined according to the highest level of change [normal, chronic gastritis, atrophic gastritis (AG), IM, or dysplasia] observed in the biopsy reports. All analyses were performed using SPSS statistics software version 19 (IBM Corporation, NY, USA). *P* values of <0.05 were considered statistically significant.

Results

We followed 1011 participants (48.9% men) for an average of 119.3 months (range: 10 to 144 months). During that time, 146 (14.4 %) subjects died and 49 (4.8 %) were lost to follow-up. Of these, 40 (3.95%) died of GC. The person-time mortality rate due to GC was 3.95 per 1000 person-years.

The cohort participants had a wide range of histological and endoscopic abnormalities other than cancer at the baseline measurement (Table 1). Chronic gastritis (either MN or PMN infiltration) was the main histological finding in 455 (46.2%) subjects. The most advanced pathological changes were AG in 333 (33.8%) and IM in 176 (17.9%) cases. Only 20 (2.0%) people had gastric biopsy specimens with completely normal histology. We did not find any cases of dysplasia in our patients.

Endoscopically, 389 (38.7%) participants had some degree of gastroesophageal reflux disease (GERD). Evidence of an active duodenal ulcer (DU) was found in 19 (1.9%) and GU was found in 30 (3.0%) participants. There were no endoscopic abnormalities in the remaining 566 (56.4%) subjects. Table 1 shows detailed information of the main demographics, risk factors, histological and endoscopic findings.

Table 2 shows the results of the Cox proportional hazard models. The univariate analysis showed an increasing trend of cancer mortality by age. Smoking, family history of GC, and the presence of GU were significant determinants of GC. Among histological changes, two well-known risk factors, AG and IM, dramatically increased the risk of death due to GC. We found no significant increase in the risk of GC mortality by gender, *H. pylori* infection, GERD or DU (Table 2).

When we fitted a multivariate hazard model by including all lifestyle demographic, endoscopic and histological factors, the HR and the 95% CIs of GC death remained significant for the 51–60 age group (4.4:1.3–15.0) and ≥61 age group (9.4:3.1–28.1). Other

Table 1. Baseline characteristics of cohort participants.

Baseline characteristics	Histological findings (*n*)				Endoscopic findings (*n*)				Total (*n*)
	Normal (20)	CG (482)	AG (333)	IM (176)	Normal (573)	DU (19)	GU (30)	GERD (389)	Total (1011)
Male (%)	30.0	50.3	42.9**	56.3**	42.9	77.8*	60*	55.5*	48.9
Mean age in years (SD)	53.7 (13.2)	51.8 (9.9)	52.7 (9.5)	57.5 (9.8)	53.1 (9.9)	55.5 (11.0)	53.1 (9.5)	55.2 (10.1)	53.1 (9.9)
H. pylori infection (%)	50.0*	89.1	95.5	83.0	87.3	94.4	93.3	88.9	88.2
Family history of GC (%)	25.0	18.7	20.7	26.7	20.4	16.7	50*	18.8	20.6
Positive smoking history (%)	25.0	38.9	36.9	45.5	39.4	61.1	46.7	37.0	39.1
Alcohol (%)	5	4.2	1.8	5.1	3.1	5.6	6.7	3.6	3.5
Illiterate (%)	79.2	70.3	79.6	81.8	76.5	83.3	70.0	74.6	75.7

GC= gastric cancer, CG= chronic gastritis, AG= atrophic gastritis, IM= intestinal metaplasia, DU= duodenal ulcer, GU= gastric ulcer, GERD= gastroesophageal reflux disease. *$P < 0.0001$ for selected item vs. otherwise, **$P < 0.0001$ for selected item vs. otherwise.

Table 2. Risk of gastric cancer (GC) represented as hazard ratios (HR) and 95% confidence intervals (CI) in univariate and multivariate Cox-regression analyses after follow-up.

Baseline characteristics		GC cases (*n*)	Univariate		Multivariate	
			HR	95% CI	HR	95% CI
Gender	Female	17	1	—		
	Male	23	1.5	0.8–2.8	—	—
Age (years)	40–50	7	1	—	1	—
	51–60	9	4.4	1.3–14.2	3.9	1.2–13.0
	≥61	24	11.0	3.8–31.7	8.0	2.7–23.5
H. pylori infection	No	8	1	—	—	—
	Yes	32	2.3	0.5–9.6		
Family history of GC	No	14	1	—	1	—
	Yes	26	7.2	3.4–14.1	6.5	3.2–13.0
Positive smoking history	No	8	1		1	—
	Yes	32	5.6	2.6–12.3	6.0	3.0–12.9
Histological finding	Normal/gastritis	25	1	—	1	—
	Atrophic gastritis (AG)	24	8.6	1.9–38.4	7.5	1.6–33.8
	Intestinal metaplasia (IM)	18	30.9	7.3–131.4	19.4	4.5–83.0
Duodenal ulcer (DU)	No	20	1	—	—	—
	Yes	20	1.5	0.2–10.8	—	—
Gastric ulcer (GU)	No	9	1	—	1	—
	Yes	31	9.1	4.0–20.1	6.0	2.4–14.0
Gastroesophageal reflux disease (GERD)	No	21	1	—	—	—
	Yes	19	1.3	0.7–2.5	—	—

risk factors, including a family history of GC, the presence of a GU and smoking were significant factors with small changes in the magnitude of the association. Again, two main histological precancerous lesions were significantly associated with a higher risk of GC compared to subjects who were either entirely normal or only had chronic gastritis. The HR and the 95% CIs were 7.4:1.6–33.8 for AG and 23.6:5.5–10.2.3 for IM (Table 2).

We found that the joint effect of individual risk factors and one of the precancerous lesions increased the HR to 46.5:10.8–198.6 for the combination of a precancerous lesion with a family history of GC, 27.6:6.5–116.4 for the combination of a precancerous lesion and smoking, and 25.1:6.3–105.3 for the combination of a precancerous lesion and age > 50 years.

Discussion

This study was conducted in a relatively large group of apparently healthy participants who resided in an area with a high incidence of GC, nearly all of whom were infected with *H. pylori*. The presence of a precancerous lesion at baseline was a strong predictor of GC mortality over long term follow-up, but age, family history of GC, smoking, and GU independently contributed to this risk. Gender, education, DU, GERD, and *H. pylori* infection did not significantly affect the risk of GC death.

Most previous studies that assessed the role of precancerous lesions used GC incidence rather than mortality as the outcome. González et al. conducted a 12.8 year follow-up in a high incidence area of Spain on symptomatic patients who referred to the hospital for gastroscopy. That study reported an incidence rate of 0.35% per year.[19] A Japanese study of male cases found a person-year incidence rate of 0.37% over a mean follow-up of 7.8 years.[20] Another study conducted in a Chinese high-risk area that enrolled only rural subjects without data on the history of GI disorders, reported an average incidence of 0.22% after a follow-up of 4.5

years.[21] We found a GC mortality rate of 3.95% during the follow-up and showed that the presence of IM and AG significantly increased mortality due to GC. The frequencies of AG and IM in the baseline assessments of our study participants were less than those in other studies. This may be related to the population-based nature of the study as most previous studies were conducted in hospital settings and on patients who presented with GI symptoms.

The relationship between peptic ulcer disease and GC is currently under debate. A previous study has shown a significant association between the presence of a GU and GC, but their subjects were drawn from hospitalized patients who had severe GI complications such as bleeding or perforation or those who had received *H. pylori* eradication therapy.[22,23] Our study showed that the presence of a previously undiagnosed GU imposed a significant risk to mortality due to GC later in life. This might support the common mechanistic link of GU and GC through AG.

Although the proportion of male patients who died of GC in our study was higher than females, the difference was not statistically significant. Male predominance of gastric adenocarcinoma has been described in a study that used the Scottish Cancer Registry records.[24] A delay in the development of intestinal type adenocarcinoma in middle-aged women might explain the male predominance. Another study has suggested that female sex hormones might induce some degree of protection against GC.[25] González et al. reported a higher risk of GC for males; however, this risk estimate was not significant after adjusting for other risk factors.[19] Lack of a significant association between male gender and the risk of GC in our regression analyses might be partly related to the masking effects of other risk factors such as smoking, AG and IM.

The robust role of family history in the risk of GC is convincing, although most of the evidence has come from case-control studies.[26] In our cohort study, we found that a family history of GC at the baseline measurement in a healthy population was strongly associated with an increased risk of GC-related death. One report reviewed 15 case-control studies of family history and GC, all of which indicated a positive relationship between these parameters, with risk ratios that ranged from 1.5- to 3.5-fold.[27] This has been attributed to genetic factors, in addition to the environmental conditions presumably shared by members of same family, which result in a familial clustering of GC. A dramatically increased risk of GC mortality in our participants with a previous or current history of smoking was another finding consistent with previous findings from the same population and other investigations that recruited different populations and various study designs.[9,28] Of note, in our study the effect of these risk factors on GC mortality was independent from the histological changes present at baseline This might suggest that these factors have an impact on the progression of precancerous lesions to GC incidence and death.

H. pylori infection did not increase GC mortality in our subjects. Similarly, González et al.[19] reported a 67.2% *H. pylori* infection rate among their study population, which did not have a significant effect on GC incidence. A lower prevalence of *H. pylori* infection and declining (non-significant) HR were reported in the more advanced lesions in their study which might be because these lesions created unfavorable conditions for helicobacter survival and thus favored the clearance of the infection.[19] The gradual disappearance of *H. pylori* in gastric mucosa saturated with advanced precancerous lesions has previously been reported in a Japanese population with a very high risk of GC.[29] Another possible explanation was related to the very high *H. pylori* infection rate and the consequent chronic gastritis in both studies, which seriously reduced the power of the studies to find any significant association. This was supported by the significantly lower rate of infection in individuals with normal baseline histology. Finally, based on previous reports, a remarkable fraction of the GCs in Ardabil arise from the cardia, which is not entirely related to *H. pylori*.[9] The lack of accurate data on tumor location in the current study does not allow us to perform separate analyses for cardia and non-cardia GCs.

The lack of a statistically significant role for *H. pylori* infection in gastric carcinogenesis in this population is challenging. We believe that our results further represent the causal relationship between *H. pylori* infection and premalignant lesions. Both AG and the IM of gastric mucosa (particularly those in non-cardia locations) are strongly associated with *H. pylori* infection.[30,31] As the other causes of AG (including autoimmune AG) are extremely rare, most cases can be considered long-term consequences of *H. pylori* infection regardless of their cross-sectional test results. A meta-analysis of seven randomized trials from high risk areas of Eastern Asia has suggested that *H. pylori* eradication reduces GC risk only in those treated at the earlier phases of carcinogenesis and before the development of pre-neoplastic lesions.[32] This strategy is not straightforward in areas like Ardabil with very high *H. pylori* infection rates. In these regions, most patients are infected at early ages, and the majority of the infected subjects are asymptomatic, thus routine testing and therapy may not be possible or appropriate. Mass eradication therapy in the general population is also not acceptable due to the side effects and the development of antibiotic-resistant microorganisms. An important breakthrough would be the development of an effective vaccine against *H. pylori* infection. Even if such a vaccine becomes available, its administration will be useful only at the very early ages and it will still be necessary to have an appropriate secondary prevention strategy for those already infected.[33,34]

This population-based study has the advantage of studying a large number of asymptomatic individuals who were followed for a relatively long time. The cohort nature of the study and the standardized endoscopy procedure with an adequate target biopsy offered the opportunity to have unbiased estimates of effect size for each of the major risk factors.

One limitation of our study is the lack of sufficient records of histological sub-types of adenocarcinoma and reliable tumor localization. As previously discussed, the proportions of intestinal to diffuse subtypes of adenocarcinoma and cardia to non-cardia sub-sites have a great impact on the interpretation of associations between cancer risk and potential risk factors. Another major limitation is that as a cohort study with a long term follow-up, there is a relatively small number of GC events. Thus we could not find significant differences between certain groups (e.g., males versus females) and the CI are rather wide for some variables.

In summary, we, through a population-based cohort study, have shown that the presence of precancerous lesions dramatically increases the rate of GC death. In particular, our findings emphasized the less recognized role of silent GU as independent risk factors for GC. Our study confirmed the independent role of advanced age, smoking, and positive family history in GC progression and mortality. We have proposed that a combined assessment of environmental risk factors, family history and precancerous lesions might be useful to identify high-risk individuals in GC early detection programs. Such combined assessments can also assist in the design of an interventional trial based on a combination of non-invasive

tests, such as pepsinogen and the urea breath test, recognize candidates for *H. pylori* eradication in infected subjects without precancerous lesions, and identify people at high risk of GC.[34–36]

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Competing interests:

The authors have declared that no competing interests exist.

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